Absence of myocardial fibrosis predicts favorable long-term survival in new-onset heart failure: A Cardiovascular Magnetic Resonance Study

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ABSTRACT

BACKGROUND

Myocardial fibrosis, identified by late-gadolinium-enhancement cardiovascular magnetic resonance (LGE-CMR), predicts outcomes in chronic heart failure (HF). Its prognostic significance in new-onset HF and reduced left ventricular ejection fraction (HF-REF) is unclear. We investigated whether the pattern and extent of fibrosis predicts survival in new-onset HF-REF of initially uncertain etiology.

METHODS AND RESULTS

Of 120 consecutive patients with new-onset (<6months) HF-REF, 31 (26%) had infarct fibrosis, 25 (21%) had midwall fibrosis, and 64 (53%) had no fibrosis. During median follow-up of 8.9 years, 33 (28%) patients died. Patients with infarct fibrosis (HR 3.32; 95% CI 1.46-7.58; P=0.004) or midwall fibrosis (HR 2.99; 95% CI 1.24-7.19; P=0.014) were more likely to die compared to those without fibrosis. On multivariable analysis, the pattern and extent of fibrosis were both associated with all-cause mortality (by fibrosis pattern: infarct: HR 2.60; 95% CI 1.08-6.27; P=0.033; midwall: HR 2.64; 95% CI 1.08-6.47; P=0.034; by fibrosis extent per 1%: HR 1.07; 95% CI 1.03-1.12; P<0.001). Fibrosis pattern also predicted composites of cardiovascular mortality or aborted sudden cardiac death (SCD) (infarct: HR 3.45; 95% CI 1.20-9.90; P=0.022; midwall: HR 6.59; 95% CI 2.26-19.22; P<0.001), and all-cause mortality, HF hospitalization or aborted SCD (infarct: HR 2.69; 95% CI 1.26-5.76; P=0.011; midwall fibrosis: HR 2.97; 95% CI: 1.37-6.45; P=0.006). Addition of fibrosis pattern to LVEF improved risk prediction for all-cause mortality (LVEFvs.LVEF+fibrosis C-statistic: 0.66vs.0.71; P=0.033). Importantly, the absence of fibrosis heralded a favorable prognosis with an 85% survival rate over the duration of follow-up.

CONCLUSIONS

The pattern and extent of myocardial fibrosis predict adverse outcomes in new-onset HF-REF. In contrast the absence of fibrosis portends a durable warranty period with a low incidence of adverse events. These findings support a role for LGE-CMR in the early risk-stratification of patients with HF of uncertain etiology.

Key Words: heart failure, late gadolinium enhancement, cardiovascular magnetic resonance imaging, myocardial fibrosis, risk stratification.

INTRODUCTION

Heart failure (HF) is a major cause of morbidity and mortality worldwide,[1] with a particularly poor prognosis in the period immediately following diagnosis.[2] Early risk stratification is important, with implications for initial treatment and intensity of follow-up. However, there remains a dearth of validated prognosticators in new-onset HF, with the majority of risk prediction tools derived from cohorts of patients with chronic HF.[3-5] Current risk stratification is heavily reliant on left ventricular ejection fraction (LVEF),[6] but the limitations of this approach are well-documented.[7, 8]

In patients with new-onset HF and reduced LVEF (HF-REF), one of the principal aims of initial evaluation is to distinguish between ischemic and non-ischemic etiologies. Late-gadolinium enhancement cardiovascular magnetic resonance (LGE-CMR) allows non-invasive detection of myocardial fibrosis,[9] and can help to differentiate between ischemic HF and non-ischemic dilated cardiomyopathy (DCM). Whereas patients with HF due to ischemic heart disease typically display a subendocardial or transmural pattern of myocardial fibrosis indicating previous myocardial infarction, patients with DCM either have no fibrosis or a characteristic midwall pattern.[9] Our group has already shown that LGE-CMR can refine and redefine diagnosis of HF etiology in newly presenting patients, thereby serving as a clinically robust and cost-effective gatekeeper to coronary angiography.[10] However, its role in the risk stratification of new-onset HF has not been elucidated.

Recent international guidelines suggest that assessment of myocardial fibrosis by LGE-CMR may aid risk stratification in selected HF patients.[11] Both the presence and extent of myocardial fibrosis on LGE-CMR predict adverse outcomes in HF patients, but specifically in those with chronic HF due to established ischemic [12-15] and non-ischemic etiologies.[16-19] There has not yet been any dedicated study of the prognostic implications of myocardial fibrosis in patients with a new diagnosis of HF-REF, in whom the underlying etiology is initially unclear. Therefore, we evaluated the prognostic significance of myocardial fibrosis in patients presenting with new-onset HF-REF of uncertain etiology.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Patients

The study prospectively enrolled 124 consecutive patients with new-onset HF (symptom onset < 6 months before CMR scan), who were referred from 6 designated HF clinics during a 2-year period. This cohort was included in an earlier report but we now present a new analysis with clinical follow-up.[10] All patients were diagnosed with HF-REF according to standard criteria.[20] Exclusion criteria included any prior known history of IHD (previous myocardial infarction or coronary revascularization), angina or significant valvular disease. Patients with contraindications to LGE-CMR were also excluded. Four patients were excluded after enrolment (two patients were unable to complete CMR examination due to claustrophobia, one patient was found to have aortic regurgitation not identified by echocardiography, one patient withdrew consent). The final cohort therefore comprised 120 patients with HF of unknown etiology and no clinical evidence of IHD. After recruitment, patients underwent coronary angiography as part of their routine clinical workup to identify significant coronary artery disease (>50% luminal stenosis in the left main vessel or >75% stenosis in either the proximal left anterior descending artery or ≥2 epicardial vessels).[21] The study was approved by the local ethics committee and all participants provided written informed consent.

CMR protocol

Cine images (Siemens Sonata 1.5T [n=42] and Siemens Avanto [n=78]) were acquired with a steady-state, free-precession, breathhold sequence (echo time/repetition time 1.6/3.2ms; flip angle 60°) in standard long-axis planes and sequential contiguous 7-mm short-axis slices (3-mm gap) from the atrioventricular ring to the apex. LGE imaging was performed 10 minutes after intravenous gadolinium-DTPA (Schering 0.1mmol/kg) in identical long- and short-axis planes using an inversion-recovery gradient echo sequence. Inversion times were adjusted to null normal myocardium (typically

280-380ms; voxel size 1.7x1.4x8.0mm) and images were obtained in 2 separate phase-encoding directions to exclude artifact.

CMR analysis

Images were analysed with semi-automated software (CMR Tools, Cardiovascular Imaging Solutions, London). A single blinded experienced reader measured right and left ventricular volumes, LVEF and left ventricular mass, using standard techniques.[22, 23] Ventricular volumes and left ventricular mass were indexed to body surface area. The presence and pattern of myocardial fibrosis was determined by a separate panel of 3 expert cardiologists blinded to all clinical data. Myocardial fibrosis was judged to be present in areas of LGE, which were visible in both phase encoding directions and two orthogonal views. Patients were categorized as having infarct fibrosis (subendocardial or transmural LGE in the distribution of a coronary artery perfusion territory), midwall fibrosis (LGE confined to the intramural and/or subepicardial layers without subendocardial involvement in any myocardial segment), or no fibrosis (**Figure 1**). In patients with infarct or midwall fibrosis, an independent reader quantified fibrosis extent as a percentage of left ventricular mass, using the full-width half-maximum technique (CMR42, Circle Cardiovascular Imaging).[24]

Clinical follow-up and end-points

Follow-up data was collected prospectively at 6 monthly intervals for all patients. Clinical events were ascertained through direct patient contact by telephone interview and postal questionnaires, review of clinical correspondence from cardiologists/family practitioners, and examination of medical records following hospitalization. Survival status was established at each follow-up interval from the UK Health and Social Care Information Service. Cause of death was ascertained from collective review of information provided by death certification, medical records for in-hospital deaths, and post-mortem results where available. No patient was lost to follow up.

The predefined primary end-point was all-cause mortality. Two secondary composite, time-to-first event, end-points were also pre-specified: 1) cardiovascular (CV) death or aborted SCD (SCD); 2) all-cause mortality, HF hospitalization or aborted SCD. CV death was defined as death due to HF, SCD, myocardial infarction, or thromboembolic event. Aborted SCD was defined as an appropriate implantable cardiiverter defibrillator (ICD) shock for ventricular arrhythmia, a non-fatal episode of ventricular fibrillation, or sustained ventricular tachycardia (>30s) causing hemodynamic compromise and requiring cardioversion. HF hospitalization was defined as a hospital admission with signs and symptoms of decompensated HF requiring intravenous HF treatment (diuretics, vasodilators and/or inotropes).

Statistical analysis

Continuous data are expressed as mean values±standard deviation, or medians with interquartile range as appropriate. The baseline characteristics of study population, stratified by fibrosis pattern, were compared by Kruskal-Wallis test for continuous variables, and Chi-squared test for categorical variables. Survival estimates were constructed by the Kaplan-Meier method. The log-rank test was used to compare the Kaplan-Meier survival curves. Univariable Cox proportional hazards models were used to analyse the relationship between baseline covariables and end points, with results presented as hazard ratios (HRs) and 95% confidence intervals (CIs). The association between fibrosis pattern/extent and outcome was evaluated in a multivariable Cox model adjusting for established prognostic variables including age, sex and LVEF. The proportional hazards assumption was tested and verified for each covariable on the basis of Schoenfield residuals. The impact of using fibrosis pattern or extent as well as LVEF to predict risk of all-cause mortality, compared to using LVEF alone, was assessed via the change in Harrell's C-Statistic using a non-parametric bootstrap approach to test the significance of the change. Stata version 15 (StatCorp, College Station, Texas) was used for all statistical analyses. A 2-tailed P value of <0.05 was considered statistically significant.

RESULTS

Study Population

One hundred and twenty patients with new-onset HF were enrolled, of whom 31 (26%) had infarct fibrosis, 25 (21%) had midwall fibrosis, and 64 (53%) had no fibrosis. The median extent of infarct fibrosis was 4.4% (interquartile range [IQR] 1.5-7.4) and the median extent of midwall fibrosis was 2.4% (IQR 1.3-4.3). No patient had co-existent infarct and midwall fibrosis. The median duration of HF at the time of enrollment was 59 days (IQR 33-88 days). **Table 1** shows the baseline characteristics of the study population stratified by fibrosis pattern. There were no significant differences in age, HF duration, functional status, CMR measures of left ventricular (LV) size and function, and prescription of disease-modifying HF medicines between the three groups at the time of CMR scanning. Patients with infarct fibrosis were more likely to receive aspirin and statin therapy at enrolment and have significant coronary artery disease.

Follow-up data

Event data are summarized in **Table 2**. Patients were prospectively followed for a median period of 8.9 years (IQR 8.3-9.5 years). During this period 35 (29%) patients had a device implanted, including 7 ICDs, 11 cardiac resynchronization therapy (CRT) pacemaker devices, and 17 CRT-defibrillators. Seventeen (14%) patients had coronary revascularization; eight had percutaneous coronary interventions (PCI), 8 had coronary artery bypass surgery (CABG), and 1 patient had both. There were 33 deaths during follow-up, of which 21 (64%) were cardiovascular, including 9 SCDs, 11 due to HF, and 1 death due to acute myocardial infarction. Twenty (17%) patients were hospitalized for HF and 6 (5%) patients had an aborted SCD.

Primary End Point: All-cause mortality

Overall, there were 33 deaths, involving 13/31 (41.9%) with infarct fibrosis and 10/25 (40.0%) patients with midwall fibrosis. In contrast, only 10/64 (15.6%) patients with no fibrosis died during this period (**Table 2**). Kaplan-Meier survival curves demonstrated an association between fibrosis pattern and all-cause mortality (**Figure 2A; Figure IA in Data Supplement**). On univariable analysis, patients with infarct fibrosis (hazard ratio [HR], 3.32; 95% confidence interval (CI), 1.46-7.58; P=0.004) and midwall fibrosis (HR, 2.99; 95% CI, 1.24-7.19; P=0.014) were more likely to reach the primary end point than those with no fibrosis (**Table 3**). In the multivariable model that included LVEF, age and sex, both infarct and midwall fibrosis remained significantly associated with all-cause mortality (infarct: HR, 2.60; 95% CI, 1.08-6.27; P=0.033; midwall: HR, 2.64; 95% CI, 1.08-6.47; P=0.034; **Table 4**). The percentage extent of fibrosis was also independently associated with the primary endpoint (HR, 1.07; 95% CI, 1.03-1.12, P=<0.001) (**Table 4)**. The prognostic significance of both fibrosis pattern and extent was retained on multivariable analysis after further adjustment for coronary revascularization or device implantation (**Table I in Data Supplement**). Addition of fibrosis assessment to a baseline model incorporating LVEF improved Harrell's C-statistic from 0.66 to 0.71 for fibrosis pattern (95% CI of difference 0.003-0.14; P=0.033), and 0.66 to 0.71 for fibrosis extent (95% CI of difference 0.00-0.14; P=0.051).

Secondary End Points

The secondary composite end point of CV death or aborted SCD occurred in 27 (23%) patients (**Table 2**), with a higher event rate among patients with infarct or midwall fibrosis (**Figure 2B; Figure IB in Data Supplement**), and only 4 CV deaths and 1 aborted SCD in the subgroup with no fibrosis. After adjusting for LVEF, age and sex, both fibrosis pattern (infarct: HR, 3.45; 95% CI 1.20-9.90; P=0.022; midwall: HR, 6.59; 95% CI, 2.26-19.22; P<0.001) and extent (HR, 1.06; 95% CI, 1.02-1.10, P=0.005) were independently associated with this outcome (**Table 4)**.

The secondary composite end point of all-cause mortality, HF hospitalization or aborted SCD, was reached by 43 (36%) patients (**Table 2**). Kaplan-Meier estimates of event-free survival again showed a significant difference in this outcome according to fibrosis pattern (**Figure 2C; Figure IC in Data Supplement**). Fibrosis pattern also predicted this outcome in the multivariable model (infarct fibrosis; HR, 2.69; 95% CI, 1.26-5.76; P=0.011; midwall fibrosis; HR, 2.97; 95% CI 1.37-6.45; P=0.006; **Table 4**), as did fibrosis extent (HR, 1.05; 95% CI, 1.01-1.09; P=0.008).

DISCUSSION

We found that the detection of myocardial fibrosis by LGE-CMR, either with infarct or midwall pattern, was associated with an increase in all-cause mortality amongst patients with new-onset HF-REF of initially undetermined etiology. The prognostic value of fibrosis was independent of LVEF, one of the most important and clinically relevant prognostic markers in current practice. Both the pattern and extent of fibrosis were also predictive of composite outcomes comprising CV mortality or aborted SCD, and all-cause mortality, aborted SCD or HF hospitalisation. Importantly, the absence of fibrosis at baseline conferred a favorable long-term prognosis with low rates of major adverse cardiovascular events. Furthermore, the combination of fibrosis pattern with LVEF improved risk prediction for all-cause mortality. These findings suggest that detection and quantification of fibrosis constitute valuable markers for early risk stratification in HF-REF irrespective of underlying etiology.

A growing body of observational evidence suggests that non-invasive fibrosis assessment by LGE-CMR constitutes a powerful tool for risk stratification in both ischemic and non-ischemic chronic HF.[25, 26] However, the vast majority of studies to date have focused on populations with established and well-characterized disease.[12-19] Patients with new-onset HF of initially uncertain etiology represent a distinct group that is frequently encountered in clinical practice. Such patients are at particularly high-risk in the early phase of their disease course, with a mortality rate 3 to 4-fold higher in the first year after diagnosis compared to subsequent years.[27-29] During the same 'high-risk' period, decisions regarding CRT and/or ICD implantation may be deferred for up to 3 months pending initiation and titration of guideline-directed medical therapy. Robust and accurate methods for risk stratification in patients with new-onset HF-REF may therefore facilitate greater individualization of treatment, enabling more aggressive strategies in patients with poorer prognosis at an earlier stage in their clinical course.

Guideline recommendations on HF treatment depend on measurement of LVEF, which is also used to stratify risk.[30, 31] However, LVEF often improves spontaneously or as a consequence of therapy in the

months following diagnosis, which may limit its prognostic utility. In one study of patients with recent-onset HF and severe ventricular dysfunction (LVEF<30%), 43% of participants demonstrated LV recovery to mildly impaired or normal function within 6 months.[32] Similarly, among patients with severe non-ischemic cardiomyopathy undergoing ICD implantation within 6 months of diagnosis, 59% no longer met guideline criteria for ICD insertion at 12 months, predominantly due to recovery of LVEF to ≥35%.[33] Prediction of outcome based solely on LVEF is therefore challenging in the early stages of HF when patients are also at the highest risk of adverse events. Similar limitation also applies to other prognostic variables such as New York Heart Association functional class, natriuretic peptides and renal function, all of which are liable to considerable fluctuation in the first year of treatment. In contrast to these dynamic indices, which may be useful for gauging response to therapy, fibrosis exhibits less variability over time.[34] Moreover, the presence and extent of fibrosis evaluated by LGE-CMR have been shown to determine the likelihood of LV reverse remodeling following therapy in patients with HF due to ischemic and non-ischemic etiologies.[34-38] Such observations reinforce the logical premise that dysfunctional myocardium with replacement fibrosis is less amenable to recovery than regions without fibrosis. We limited our investigation to patients with recently diagnosed HF-REF, a substantial proportion of whom might be expected to experience LV reverse remodeling with optimal treatment. Our findings highlight the prognostic value of LGE-CMR in this group, and suggest that myocardial fibrosis assessment may serve as a more stable and durable marker of risk in the early stages of HF after diagnosis.

A number of mechanisms may underpin the relationship between fibrosis and adverse outcomes. It is well recognized that myocardial fibrosis provides a substrate for ventricular re-entrant arrhythmia and hence SCD.[39, 40] In addition, since myocardial fibrosis is closely linked to the likelihood of reverse remodeling, it may provide a marker of the severity of the intrinsic pathologic processes driving ventricular dysfunction and HF progression. Infarct fibrosis has been shown to correlate with the underlying burden of coronary artery disease and may therefore also signify overall atherosclerotic risk.[12]

We found that myocardial fibrosis detection offered independent and incremental prognostic information for all-cause mortality. These findings accord with previous studies of LGE-CMR. Amongst 61 patients with advanced HF due to new-onset non-ischemic DCM, midwall fibrosis detected by LGE-CMR was a strong predictor of subsequent death or the need for cardiac transplantation or mechanical circulatory support.[41] The presence of fibrosis was also associated with a range of adverse cardiovascular outcomes in two further cohorts of patients with suspected non-ischemic cardiomyopathy of recent onset.[42, 43] Although these studies support the potential prognostic value of LGE-CMR in the early evaluation of HF, they were limited by small sample sizes and / or short duration of follow-up, leading to reliance on broad composite endpoints. In contrast, the prolonged follow-up and greater number of events in the present study allowed us to demonstrate the prognostic impact of fibrosis on overall survival alone, as well as important non-fatal events. Perhaps the most remarkable finding from our study was the ability of LGE-CMR to identify a cohort of HF-REF patients with a low long-term risk of adverse cardiovascular outcomes. In patients without CMR evidence of fibrosis, overall survival over a median of 9 years was 85%. Indeed, there were numerically more deaths due to non-cardiovascular causes in the subgroup without myocardial fibrosis, reflecting the increased exposure to competing risks that accrues with improved survival.

In the diagnostic work-up of HF, ischemic LV dysfunction is conventionally distinguished from DCM by the presence of >50% stenosis in one or more epicardial coronary arteries.[44] Previous work by our group has questioned the validity of this simple dichotomous approach and formed the basis for a more refined etiologic classification informed by myocardial fibrosis assessment using LGE-CMR, in addition to luminal angiography.[10] The present study now establishes the prognostic implications of these tissue characterization findings. Historically, HF of ischemic etiology has been associated with a poorer prognosis than non-ischemic cardiomyopathy. Yet we observed that the risk of all-cause mortality and adverse cardiovascular outcomes among DCM patients with midwall fibrosis was at least equivalent to patients with prior infarction. These findings concur with a previous investigation, which showed that patients with DCM who exhibited midwall fibrosis had a similar risk of adverse events to those with ischemic cardiomyopathy following CRT implantation, whilst DCM patients

without fibrosis had a far superior prognosis.[45] Moreover in the present study, the extent of fibrosis (irrespective of pattern) predicted outcome, suggesting that the burden of myocardial scar is an important prognostic factor regardless of HF etiology.

Such observations are of particular interest in light of recent evidence from the DANISH trial that has questioned the benefit of prophylactic ICD implantation in DCM.[46] The lack of observed benefit from ICD implantation in that trial (which did not use LGE-CMR to select patients) has been attributed, in large measure, to the more favorable prognosis of DCM compared to ischemic cardiomyopathy.[47] Although the present study was not powered to study the impact of fibrosis on SCD *per se*, it clearly suggests that LGE-CMR may be able to identify a subset of DCM patients with an adverse prognosis and an overall risk profile akin to ischemic cardiomyopathy. The potential contribution of LGE-CMR to stratification of SCD risk in non-ischemic cardiomyopathy has recently been recognized in major international guidelines.[11] Given the strong prognostic signal demonstrated in this and other studies, prospective trials are now warranted to examine whether fibrosis imaging can improve clinical outcomes in HF by guiding prophylactic ICD implantation.[48]

Study limitations

The study population size and event rate limited the number of candidate covariables we could include in our multivariable model. In addition, several well-established prognostic factors in HF, including renal function and natriuretic peptide levels, were not systematically recorded in all patients and not included in our analyses. Further work in larger cohorts is required to assess the incremental value of fibrosis over these and other markers both individually, and as part of validated multivariable prognostic scoring systems. We acknowledge that a single tertiary centre CMR unit has the potential to attract referral bias. However, we tried to minimize the risk of this by enrolling consecutive patients with newly presenting HF-REF at 5 additional secondary care institutions without in-house CMR. Our study cohort consisted predominantly of patients with mild to moderate HF in sinus rhythm and without clinical features suggestive of IHD. Whilst the population has broad relevance to clinical practice, our findings may not be applicable to patients with more severe or advanced HF. In

particular the rate of SCD or aborted SCD in our cohort was relatively low, reflecting the spectrum of disease severity and high rates of contemporary medical therapy. LGE-CMR detects focal regions of replacement fibrosis. Patients with HF-REF may also exhibit diffuse interstitial fibrosis. Emerging CMR T1-mapping techniques were not in routine clinical use at the inception of the study, but may allow quantification of interstitial fibrosis.

Conclusions

In patients with HF of recent onset and uncertain etiology, the detection of infarct pattern or midwall myocardial fibrosis by LGE-CMR provides prognostic information independent of that provided by age, sex and LVEF, and improves risk stratification for all-cause mortality. These findings provide an additional rationale for LGE-CMR in this clinical setting beyond its established diagnostic utility. Further study is now required to explore whether changes in management based on knowledge of fibrosis pattern and extent for patients with new-onset HF-REF can improve outcomes.

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DISCLOSURES

Dr Morarji is currently employed by Pfizer. Professor Pennell has served as a consultant for and Siemens and is a director and shareholder of Cardiovascular Imaging Solutions. Dr Prasad has received honoraria from Schering. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

CLINICAL PERSPECTIVE

Risk stratification of patients with new-onset heart failure and reduced left ventricular ejection fraction (HF-REF) is challenging because many established prognostic markers, including left ventricular ejection fraction (LVEF), are liable to change substantially in response to guideline-directed heart failure therapies. Identification of more stable and durable markers of long-term risk in the initial months following diagnosis may help guide the use of more intensive treatment strategies, such as device therapy, at an earlier stage in disease trajectory. Myocardial fibrosis, identified by late gadolinium enhancement cardiovascular magnetic resonance (LGE-CMR), has previously been shown to predict outcomes in established HF-REF. In this study, we show that myocardial fibrosis assessment by a single baseline LGE-CMR in patients with new-onset HF-REF provides powerful prognostic information over a protracted period. Even after adjustment for LVEF, patients with myocardial fibrosis, in either an infarct or midwall pattern, had a 2 to 3-fold increased risk of all-cause mortality. The absence of fibrosis portends a significant warranty period, with an 85% survival rate over a median of 9-years follow-up observed in our cohort. Our findings provide evidence that LGE-CMR could help to inform decision-making in new-onset HF-REF patients regarding advanced HF therapies and treatments for other major co-morbidities.

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TABLE LEGENDS

Table 1. Baseline Characteristics of the Study Group According to Fibrosis Pattern.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II-receptor blocker; CAD, coronary artery disease; HF, heart failure; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association; RV, right ventricular; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systolic volume.

*Variable was not normally distributed and is presented as median (upper quartile, lower quartile).

Table 2. Study Outcome Data According to Fibrosis Pattern.

HF denotes heart failure.

*The number of patients who experienced an index composite outcome is stated.

Table 3. Hazard Ratios for All-Cause Mortality in Univariable Analysis.

CAD indicates coronary artery disease; CI, confidence interval; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association; RV, right ventricular; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systolic volume.

Table 4. Hazard Ratios for Primary and Secondary End Points in Multivariable Analysis

*In multivariable model 1, fibrosis pattern was included as a covariable.

†In multivariable model 2, fibrosis percentage extent was included as a covariable.

CI indicates confidence interval; HF, heart failure; SCD, sudden cardiac death; LVEF, left ventricular ejection fraction.

FIGURE LEGENDS

Figure 1. Fibrosis Patterns Identified by Late Gadolinium Enhancement Cardiovascular Magnetic Resonance in Patients with New-Onset Heart Failure. A&B: Subendocardial late gadolinium enhancement (LGE) in the lateral and inferior walls indicating infarct fibrosis. **C&D:** Midwall LGE of the septum indicating midwall fibrosis. **E&F:** No LGE in a patient with no detectable replacement fibrosis.

Figure 2. Kaplan-Meier Estimates of the time to All-Cause Mortality (A), Cardiovascular Death or Aborted Sudden Cardiac Death (B), and All-Cause Mortality, Heart Failure Hospitalization or Aborted Sudden Cardiac Death (C), According to Fibrosis Pattern.

TABLES

Table 1.

Characteristics	All patients (n=120)	Infarct fibrosis (n=31)	Midwall fibrosis (n=25)	No fibrosis (n=64)	P value
Age,yr	56.8±11.2	59.8±10.6	53.2±11.7	56.8±11.0	0.087
Male sex,n(%)	96 (80.0)	29 (93.6)	21 (84.0)	46 (71.9)	0.035
HF duration,days*	59 (34,88)	46 (15,75)	50 (30,93)	65 (42,94)	0.07
Diabetes,n(%)	20 (16.7)	9 (29.0)	2 (8.0)	9 (14.1)	0.099
Hypertension,n(%)	56 (46.7)	19 (61.3)	5 (20.0)	32 (50.0)	0.006
Hypercholesterolemia,n(%)	37 (30.8)	13 (41.9)	7 (28.0)	17 (26.6)	0.33
Smoker,n(%)	29 (24.2)	11 (35.5)	3 (12.0)	15 (23.4)	0.13
Flu/coryzal symptoms,n(%)	11 (9.2)	3 (9.7)	2 (8.0)	6 (9.4)	1.00
History of alcohol excess,n(%)	7 (5.8)	1 (3.2)	2 (8.0)	4 (6.3)	0.88
Significant CAD,n(%)	27 (22.5)	23 (74.2)	1 (4.0)	3 (4.7)	<0.001
NYHA functional class,n(%)					
I	29 (24.2)	7 (22.6)	10 (40.0)	12 (18.8)	0.13
II	75 (62.5)	17 (54.8)	13 (52.0)	45 (70.3)	
III	16 (13.3)	7 (22.6)	2 (8.0)	7 (10.9)	
Medications at baseline,n(%)					
Aspirin	56 (46.7)	20 (64.5)	15 (60.0)	21 (32.8)	0.004
Warfarin	11 (9.2)	2 (6.5)	4 (16.0)	5 (7.8)	0.44
Beta-blocker	84 (70.0)	21 (67.7)	18 (72.0)	45 (70.3)	0.93
ACE-inhibitor or ARB	110 (91.7)	29 (93.6)	22 (88.0)	59 (92.2)	0.75
Statin	56 (46.7)	20 (64.5)	12 (48.0)	24 (37.5)	0.048
Loop diuretic	73 (60.8)	20 (64.5)	17 (68.0)	36 (56.3)	0.56
Aldosterone antagonist	24 (20.0)	7 (22.6)	7 (28.0)	10 (15.6)	0.36
Cardiovascular Magnetic Resonance measurements					
LVEDV index,ml/m^2	124.0±43.5	128.3±56.9	137.1±47.1	116.7±32.4	0.22
LVESV index,ml/m^2	80.3±44.8	85.8±58.7	94.2±47.4	72.3±33.8	0.11
LV stroke volume,ml	87.3±29.1	85.0±26.6	85.9±21.6	88.9±32.9	0.90
LVEF,%	39.0±13.5	37.2±14.2	35.1±12.0	41.3±13.4	0.075
LV mass index,g/m^2	107.6±33.9	103.5±28.9	111.6±41.6	108.0±33.2	0.83

RVEDV index,ml/m^2	81.0±24.4	80.9±26.7	81.6±23.6	80.8±23.9	0.92
RVESV index,ml/m^2	38.3±20.3	40.3±22.7	40.8±18.3	36.3±20.0	0.22
RV stroke volume,ml	85.6±27.8	81.3±27.0	81.5±17.7	89.3±31.0	0.24
RVEF,%	54.4±12.8	51.9±12.7	51.7±9.7	56.6±13.6	0.020
Fibrosis extent,%*		4.4 (1.5,7.4)	2.4 (1.3,4.3)		

Table 2.

Outcome	All patients (n=120)	Infarct fibrosis (n=31)	Midwall fibrosis (n=25)	No fibrosis (n=64)
Primary end point, n(%)				
All-cause mortality	33 (27.5)	13 (41.9)	10 (40.0)	10 (15.6)
Secondary end points, n(%)				
Cardiovascular death or aborted sudden cardiac death*	27 (22.5)	10 (32.3)	12 (48.0)	5 (7.8)
Cardiovascular Death	21 (17.5)	9 (29.0)	8 (32.0)	4 (6.3)
Aborted Sudden Cardiac Death	6 (5.0)	1 (3.2)	4 (16.0)	1 (1.6)
All-cause mortality, HF hospitalization or aborted sudden cardiac death*	43 (36.1)	16 (51.6)	13 (54.2)	14 (21.9)
Heart failure hospitalisation	20 (16.7)	8 (25.8)	5 (20.0)	7 (10.9)
Device implantation				
Implantable cardioverter-defibrillator	7 (5.8)	3 (9.7)	2 (8.0)	2 (3.1)
Cardiac resynchronisation therapy without defibrillator	11 (9.2)	2 (6.5)	3 (12.0)	6 (9.4)
Cardiac resynchronisation therapy with defibrillator	17 (14.2)	4 (12.9)	6 (24.0)	7 (17.2)
Coronary revascularization				
Percutaneous coronary revascularization	9 (7.5)	7 (22.6)	0 (0)	2 (3.1)
Coronary artery bypass graft surgery	9 (7.5)	8 (25.8)	0 (0)	1 (1.6)

Table 3.

	Univariable Analysis		
Variable	**Unadjusted Hazard Ratio (95% CI)**	**X^2**	**P value**
Age,per 10 years increase	1.34 (0.98-1.85)	3.43	0.068
Male sex	1.52 (0.59-3.93)	0.81	0.39
Diabetes	1.74 (0.78-3.86)	1.67	0.17
Hypertension	0.85 (0.42-1.69)	0.23	0.63
Hypercholesterolemia	1.01 (0.48-2.12)	0.0003	0.99
Smoker	1.08 (0.49-2.40)	0.04	0.85
Flu/coryzal symptoms	0.92 (0.28-3.00)	0.02	0.88
History of alcohol excess	1.75 (0.53-5.75)	0.73	0.36
Significant CAD	2.16 (1.04-4.45)	3.90	0.038
NYHA functional class	1.91 (1.04-3.49)	4.42	0.036
LVEDV index,per 10ml/m^2 increase	1.08 (1.01-1.15)	4.40	0.019
LVESV index,per 10ml/m^2 increase	1.09 (1.03-1.15)	6.69	0.003
LV stroke volume,per 10ml decrease	1.14 (1.00-1.30)	3.93	0.056
LVEF,per 5% decrease	1.22 (1.07-1.39)	9.55	0.002
LV mass index,per 10g/m^2 increase	1.01 (0.91-1.12)	0.03	0.55
RVEDV index,per 10ml/m^2 increase	0.96 (0.83-1.12)	0.25	0.62
RVESV index,per 10ml/m^2 increase	1.12 (0.97-1.29)	2.04	0.13
RV stroke volume,per 10ml decrease	1.23 (1.07-1.42)	7.97	0.005
RVEF,per 5% decrease	1.21 (1.08-1.37)	9.32	0.002
Fibrosis pattern			
No fibrosis	1.00		
Infarct fibrosis	3.32 (1.46-7.58)	10.33	0.004
Midwall fibrosis	2.99 (1.24-7.19)		0.014
Fibrosis extent,per 1% increase	1.07 (1.04-1.11)	11.90	<0.001

Table 4.

		Model 1*		Model 2†	
		Adjusted Hazard Ratio		Adjusted Hazard Ratio	
Outcome	**Variable**	**(95% CI)**	**P value**	**(95% CI)**	**P value**
All-cause mortality	LVEF,per 5% decrease	1.19 (1.05-1.35)	0.006	1.17 (1.03-1.33)	0.017
	Age,per 10 years increase	1.38 (0.99-1.94)	0.061	1.47 (1.07-2.02)	0.017
	Male sex	1.43 (0.51-4.03)	0.50	1.32 (0.48-3.63)	0.59
	Fibrosis pattern				
	No fibrosis	1.00			
	Infarct fibrosis	2.60 (1.08-6.27)	0.033		
	Midwall fibrosis	2.64 (1.08-6.47)	0.034		
	Fibrosis extent,per 1% increase			1.07 (1.03-1.12)	<0.001
Cardiovascular death or aborted SCD	LVEF,per 5% decrease	1.27 (1.11-1.45)	<0.001	1.28 (1.12-1.47)	<0.001
	Age,per 10 years increase	1.25 (0.84-1.85)	0.27	1.19 (0.81-1.75)	0.37
	Male sex	1.91 (0.63-5.78)	0.25	2.05 (0.61-6.91)	0.25
	Fibrosis pattern				
	No fibrosis	1.00			
	Infarct fibrosis	3.45 (1.20-9.90)	0.022		
	Midwall fibrosis	6.59 (2.26-19.22)	<0.001		
	Fibrosis extent,per 1% increase			1.06 (1.02-1.10)	0.005
All-cause mortality, HF hospitalization or aborted SCD	LVEF,per 5% decrease	1.16 (1.05-1.29)	0.005	1.16 (1.03-1.29)	0.011
	Age,per 10 years increase	1.23 (0.93-1.64)	0.15	1.28 (0.97-1.68)	0.076
	Male sex	1.60 (0.64-3.97)	0.31	1.62 (0.66-4.00)	0.29
	Fibrosis pattern				
	No fibrosis	1.00			
	Infarct fibrosis	2.69 (1.26-5.76)	0.011		
	Midwall fibrosis	2.97 (1.37-6.45)	0.006		
	Fibrosis extent,per 1% increase			1.05 (1.01-1.09)	0.008

FIGURES

Figure 1.

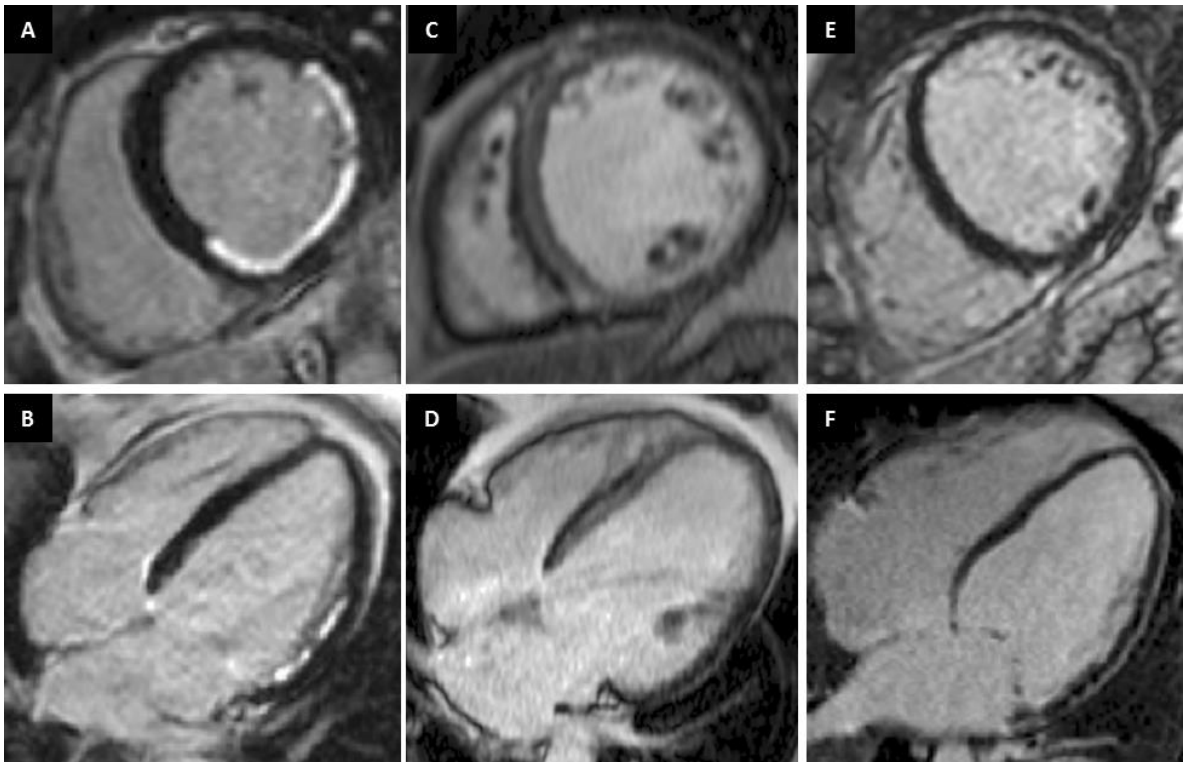
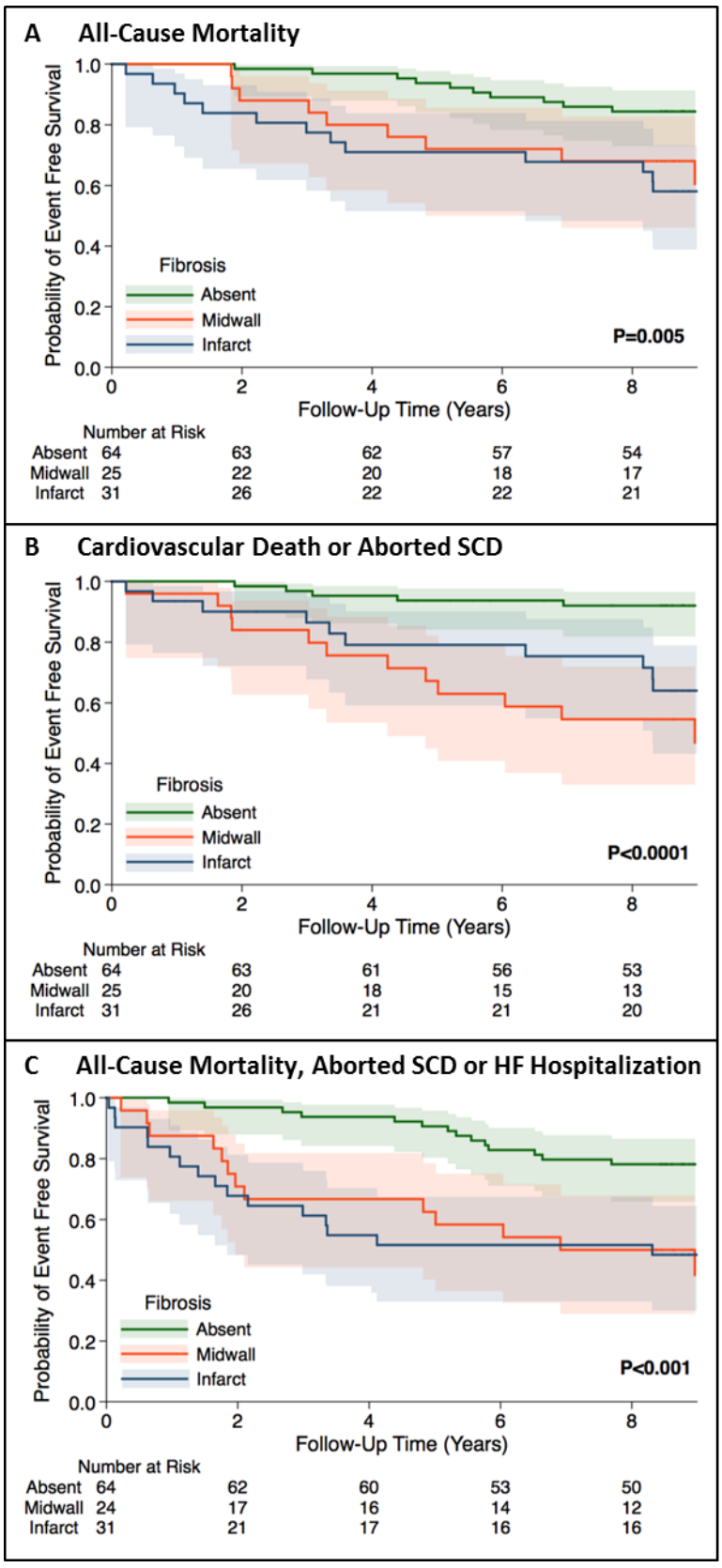


Figure 2.


A All-Cause Mortality
Probability of Event Free Survival
1.0
0.8
0.6
0.4
0.2
0.0
Fibrosis
Absent
Midwall
Infarct
P=0.005
0
2
4
6
8
Follow-Up Time (Years)
Number at Risk
Absent 64 63 62 57 54
Midwall 25 22 20 18 17
Infarct 31 26 22 22 21
B Cardiovascular Death or Aborted SCD
Probability of Event Free Survival
1.0
0.8
0.6
0.4
0.2
0.0
Fibrosis
Absent
Midwall
Infarct
P<0.0001
0
2
4
6
8
Follow-Up Time (Years)
Number at Risk
Absent 64 63 61 56 53
Midwall 25 20 18 15 13
Infarct 31 26 21 21 20
C All-Cause Mortality, Aborted SCD or HF Hospitalization
Probability of Event Free Survival
1.0
0.8
0.6
0.4
0.2
0.0
Fibrosis
Absent
Midwall
Infarct
P<0.001
0
2
4
6
8
Follow-Up Time (Years)
Number at Risk
Absent 64 62 60 53 50
Midwall 24 17 16 14 12
Infarct 31 21 17 16 16

SUPPLEMENTAL MATERIAL

Absence of myocardial fibrosis predicts favorable long-term survival in new-onset heart failure: A Cardiovascular Magnetic Resonance Study

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Online Data Supplement

Table of Contents

Table I. Hazard Ratios for All-Cause Mortality in Multivariable Analysis including Coronary Revascularization (A) or Device Implantation (B) as Candidate Variables

A

		Model 1*		Model 2†	
		Adjusted Hazard Ratio		Adjusted Hazard Ratio	
Outcome	Variable	(95% CI)	P value	(95% CI)	P value
All-cause mortality	LVEF, per 5% decrease	1.21 (1.07, 1.36)	0.002	1.19 (1.06, 1.33)	0.004
	Age, per 10 years increase	1.37 (0.94, 1.98)	0.10	1.63 (1.12, 2.37)	0.011
	Male sex	1.50 (0.55, 4.14)	0.43	1.60 (0.63, 4.08)	0.32
	Coronary Revascularization	0.31 (0.08, 1.20)	0.091	0.28 (0.07, 1.15)	0.078
	Fibrosis pattern				
	No fibrosis	1			
	Infarct fibrosis	2.53 (1.09, 5.90)	0.031		
	Midwall fibrosis	4.15 (1.58, 10.88)	0.004		
	Fibrosis extent, per 1% increase			1.10 (1.06, 1.13)	<0.0001

B

		Model 1*		Model 2†	
		Adjusted Hazard Ratio		Adjusted Hazard Ratio	
Outcome	Variable	(95% CI)	P value	(95% CI)	P value
All-cause mortality	LVEF, per 5% decrease	1.18 (1.05, 1.32)	0.005	1.16 (1.03, 1.31)	0.012
	Age, per 10 years increase	1.36 (0.94, 1.97)	0.098	1.45 (1.02, 2.07)	0.039
	Male sex	1.38 (0.48, 3.94)	0.55	1.29 (0.51, 3.27)	0.59
	ICD/CRT implantation	1.36 (0.62, 2.98)	0.44	1.33 (0.64, 2.76)	0.44
	Fibrosis pattern				
	No fibrosis	1			
	Infarct fibrosis	2.49 (1.03, 5.96)	0.041		
	Midwall fibrosis	2.57 (1.05, 6.25)	0.038		
	Fibrosis extent, per 1% increase			1.07 (1.03, 1.12)	0.001

* In multivariable model 1, fibrosis pattern was included as a covariable.

† In multivariable model 2, fibrosis percentage extent was included as a covariable.

CI indicates confidence interval; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction.

Figure I. Kaplan-Meier Estimates of the time to All-Cause Mortality (A), Cardiovascular Death or Aborted Sudden Cardiac Death (B), and All-Cause Mortality, Heart Failure Hospitalization or Aborted Sudden Cardiac Death (C), stratified by Fibrosis Pattern after adjustment for Age, Sex, and Left Ventricular Ejection Fraction.